IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Rodriguez et al.	)	
Serial No.: 10/051662	)	Examiner: R. Cook
Filed: January 18, 2002	)	Group Art Unit: 1614
For: Prevention of Ovarian Cancer by Administration of a Vitamin D Compound	)	

DECLARATION OF JEAN A. HURTEAU

1. I, Jean A. Hurteau, I am a board-certified Gynecologic Oncologist, specializing in surgical and chemotherapeutic management of women with gynecologic cancers, as well as research relating to gynecologic oncology, including ovarian cancer. I am also board-certified in obstetrics and gynecology.

2. I am currently a Professor in the Department of Obstetrics and Gynecology at the University of Illinois in Chicago. I am the Director of the Division of Gynecologic Oncology in the Department of Obstetrics and Gynecology at the University of Illinois in Chicago.

3. In 1985, I graduated from University of Montreal, obtaining the degree of Doctor of Medicine (MD). From 1985-1990, I received residency training at Obstetrics and Gynecology at University of Toronto. From 1992-1995, I received specialty training in Gynecologic Oncology at Duke University. Since 1990, I have been continuously engaged in research and development activities relating to gynecologic oncology, including ovarian cancer.

4. I have reviewed the pending patent application Serial No. 10/051,662 ("the Rodriguez application"). I have also reviewed the Office Action from the Patent Office dated October 26, 2004. I have focused on Pages 3-4 of the Office Action under the section entitled

"Claim Rejections - 35 U.S.C. §112."

5. In the first paragraph of that section, the Patent Office states the following:

> Claims 35-38, 45-46, 49, 55-57, 59, 65-71 and 73 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "appropriate" doses (specification, page 15) of 1,25-dihydroxyvitamin D_3 does not reasonably provide enablement for any and all doses. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. ***Goodman and Gilman (pages 1584-1587) disclose that some of the doses disclosed in the specification and recited in the claims cause Vitamin D toxicity.***

(emphasis added).

6. I reviewed the pages from Goodman and Gilman (pages 1584-1587) cited by the Patent Office. In my opinion, while the teachings in Goodman and Gilman (hereinafter referred to as "Goodman") may have represented the understanding of the art on Vitamin D toxicity in 1975, those teachings do not represent the state of the art currently or as of 1997, when the parent application to this application was filed.

7. I will first discuss pages 1584-1587 from Goodman cited by the Patent Office. On page 1585, the Goodman authors state:

> There is wide individual variation in the amount of vitamin D that causes hypervitaminosis. As a rough approximation, it may be stated that the continued ingestion of 50,000 units or more daily by a person with normal vitamin D sensitivity may result in poisoning.

I note that Goodman states "50,000 units or more ***daily by a person with normal Vitamin D sensitivity may result in poisoning.***" They key word here is "daily." Goodman also states on page 1585 that "700 to 2500 units daily in adults may raise the plasma cholesterol level."

8. As an initial matter, I note that the cited Goodman and Gilman reference

was published in 1975, over 20 years before the filing date of the Rodriguez application. Since 1975, we have learned much about the toxicity of Vitamin D. In fact, the Rodriguez application discloses a key teaching regarding the high dosing of Vitamin D to avoid toxicity. Specifically, the Rodriguez application teaches that one skilled in the art can avoid toxicity at high dosages by administering the higher dosages on a schedule that is less frequent than daily. Pages 16-17 of the Rodriguez application teaches:

> Prophylactic regimens for administration of Vitamin D compounds for normal female individuals and for those at increased risk of ovarian epithelial cancer can ***include daily or other periodic administration*** of Vitamin D compounds. It is contemplated that preferred regimens for prevention of ovarian cancer may comprise periodic administration of ***relatively larger dosages*** of Vitamin D compounds on ***a monthly or less than monthly basis rather than more frequent administration***.... The advantage of a technique of using large doses of Vitamin D on an infrequent basis is that it may minimize the adverse calcemic effects of a more frequent administration of Vitamin D compounds.

This disclosure would enable persons skilled in the art to practice at dosages that Goodman and Gilman believed to be potentially toxic in 1975. The Rodriguez application teaches that one can provide dosages at these high levels by pulsing on a basis of less frequent than daily. For example, a high dosage like this could be administered on a once per month basis.

9. Based on what is taught in the Rodriguez application in 1997, a person skilled in the art could practice the invention for the full range of the claims. One would administer high dosages on a basis of less frequent than daily, such as a monthly basis. Also, there are well known tests to monitor patients for hypercalcemia and other types of Vitamin D toxicity. These tests are both well known and commonly administered by persons skilled in the art. Persons skilled in the art could therefore easily apply dosages and administer them either on a daily basis or on a less frequent basis, and monitor the patient for hypercalcemia.

10. In fact, I note that on page 1587 of the Goodman reference it states that capsules of 50,000 U.S.P. units are commercially available for Vitamin D_2. Further, on page 1588, the Goodman reference states that dosages of up to ***200,000 U.S.P. units*** of Vitamin D_3 are administered ***on a daily basis*** for some treatments. This can be accomplished by monitoring the patient as I described in the preceding paragraph.

11. Various publications confirm the teaching of the Rodriguez application that one can administer far higher dosages of Vitamin D_3 by dosing on a basis of less frequent than daily. For example, the following publications confirm that high dosages of Vitamin D_3 can be safely administered by dosing on a less frequent than daily basis: (1) Beer TM, Lemmon D, Lowe BA, Henner WD, *High-dose weekly oral calcitriol in patients with a rising PSA after prostatectomy or radiation for prostate carcinoma,* Cancer 2003;97(5):1217-24; (2) Beer TM, Hough KM, Garzotto M, Lowe BA, Henner WD, *Weekly high-dose calcitriol and docetaxel in advanced prostate cancer. Seminars in Oncology* 2001;28(4 Suppl 15):49-55; (3) Beer TM, Munar M, Henner WD, *A Phase I trial of pulse calcitriol in patients with refractory malignancies: pulse dosing permits substantial dose escalation,* Cancer 2001;91(12):2431-9; and (4) Smith DC, Johnson CS, Freeman CC, et al., *A Phase I trial of calcitriol (1, 25-dihydroxycholecalciferol) in patients with advanced malignanc,* Clinical Cancer Res 1999;5(6):1339-45.

12. In addition, the Rodriguez application teaches that Vitamin D analogs can be administered at even higher dosages without inducing the deleterious side affects of Vitamin D_3, such as hypercalcemia. Specifically, the Rodriguez application states at page 16:

> It is hypothesized that even higher dosages of 1,25-dihydroxyvitamin D_3 may be more effective in inducing apoptosis. A Vitamin D analogue that has greater potency than 1,25-dihydroxyvitamin D_3 in inducing apoptosis and/or which does not

> have the deleterious side effects of 1,25-dihydroxyvitamin D_3, such as hypercalcemia, could be administered at a dosage equivalent much higher than 1.0 mg/kg of 1,25-dihydroxyvitamin D_3. While the potency and bioavailability of other Vitamin D compounds and analogues may vary, those of skill in the art can determine their apoptotic potency in relation to 1,25-dihydroxyvitamin D_3 and appropriate dosages and regimens of administration through use of in vitro testing methods such as disclosed in the accompanying example.

13. Indeed, the Rodriguez application states at pages 21-22 that the particular dosage that would be appropriate for an individual would be readily within the knowledge of the person skilled in the art given the teachings of the application:

> Those of ordinary skill in the art will readily optimize effective dosages and concurrent administration regimens as determined by good medical practice and the clinical condition of the individual patient. Regardless of the manner of administration, the specific dose may be calculated according to body weight, body surface area or organ size. Further refinement of the calculations necessary to determine the appropriate dosage for treatment involving each of the above mentioned formulations is routinely made by those of ordinary skill in the art and is within the ability of tasks routinely performed by them without undue experimentation, especially in light of the dosage information and assays disclosed herein. Appropriate dosages may be ascertained through use of established assays for determining dosages in conjunction with appropriate dose-response data. The final dosage regimen will be determined by the attending physician, considering various factors which modify the action of drugs, e.g. the drug's specific activity, the responsiveness of the subject, the age, condition, body weight, diet and sunlight exposure of the patient, the severity of any infection, time of administration and other clinical factors. Given the teachings herein those of ordinary skill would be able to determine appropriate dosage levels of Vitamin D compounds for inducing apoptosis of non-neoplastic ovarian epithelial cells.

14. I also address another issue from the Office Action dated October 26, 2004, namely the issue relating to estranes and gonanes as progestins. Page 4 of Office Action reads as follows:

> Claims 36-38, 46, 49 55-57, 59, 65-71 and 73 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out or distinctly claim the subject matter which applicant regards as the invention.
>
> Claims 36-38, 46, 49, 55-57, 59, 65-71 and 73 are confusing to the extent that they read on estranes and gonanes, since it is not seen that estranes or gonanes are progestin compounds. Hackh's Chemical Dictionary defines gonane as the steroid parent structure. Goodman and Gilman disclose that estranes (estrogens) are distinct from progestins.

The references cited by the Patent Office are from 1969 and 1975.

15. It was well known in the art by 1997, and now, that in the field of progestins, such there are subclasses of progestins known as estranes, gonanes and pregnanes. For example, the book entitled "*Progestins and Antiprogestins in Clinical Practice*," published in 2000, includes a chapter entitled "Pharmacology of Progestins: 17 Alpha Hydroxy Progesterone Derivatives and Progestins in the First and Second Generation."

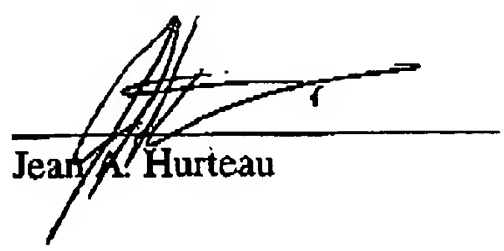
16. Turning first to the issue of estranes, subsection V of that chapter is entitled "***Estranes: the First-Generation Progestins***." Subsection V includes a discussion of the estranes that are progestins. Specifically, as noted in that subsection, the "estrane progestins are derivatives of the testosterone molecule." (page 109 of).

17. The next subsection of the chapter is entitled "***Gonane Progestins of the Second Generation.***" This subsection includes a discussion of the gonanes that are progestins. As explained in that subsection, the "gonane progestins are divided into two classes called the second and third generations." (page 113).

18. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statement were made with the knowledge that willful false statements and the like so

made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date 4/24/05



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